REMARKS/ARGUMENTS

Pending claims

Currently pending in this application are claims 1-13, 17-18, 22-24, and 26.

Rejection of Claims Under 35 U.S.C. 103(a) over Pirrung and Gallop

Claims 10-13, 17-18, and 20-26 [sic] stand rejected under 35 U.S.C. 103(a) as being unpatentable over the Pirrung et al. Advance ACS Abstract ("Pirrung") and Gallop et al. Journal of Medicinal Chemistry ("Gallop") references cited in previous Office Actions. Applicants respectfully contend that this rejection is improper and should be withdrawn.

The Examiner states that the Pirrung reference teaches a "non-peptide 'Indexed' library" and that the compounds of Pirrung are carbamates. In addition, the Examiner cites Pirrung as teaching that the compounds of the indexed libraries are generated in free form (as a mixture) and that the most active member of the library can be deduced by preparing and screening sublibraries (mixtures) of compounds. However, the Examiner admits that Pirrung does not teach "500 different compounds in 500 reaction vessels and substantially a single compound in each vessel."

The Examiner states that the Gallop reference "review[s] combinatorial techniques and screening methods," that Gallop teaches "that the 'split synthesis' algorithm is easily adapted to generating equimolar mixtures of soluble peptides," and further states that "it would have been obvious to one skilled in the art to prepare a combinatorial library of 500 different compounds using the formula given by Gallop." However, the Examiner does not state that the Gallop reference teaches or suggests the synthesis of compounds in reaction vessels in which each reaction vessel contains substantially only one compound, as required by the pending claims.

The Examiner then states that "it would have been obvious to a person skilled in the art . . . to use the split method of synthesis of **soluble peptides** taught by Gallop et al with indexed library synthesis method taught by Pirrung et al and use 500 different vessels to obtain 500 different compounds in the library." (emphasis in original) The Examiner continues,

> A person skilled in the art would have been motivated to use the indexed library of Pirrung et al to synthesize a combinatorial library of 500 different compounds in 500 reaction vessels or wells because Pirrung et al teach that the method can be prepared using any class of compounds and can be used for any type of assay because all compounds are generated in a free form and Gallop et al teach the advantages of use combinatorial library of compounds in drug discovery.

Applicants respectfully traverse this rejection. As a preliminary matter, Applicants reiterate that the Pirrung reference is not an enabling disclosure for the teachings cited by the

Examiner. However, even if the Pirrung reference were an enabling disclosure, the Examiner's arguments are not correct. Neither the Pirrung reference nor the Gallop reference teach or suggest the claimed methods, in which, *inter alia*, arrays of compounds in solution are formed in reaction vessels and each reaction vessel contains substantially only one compound.

As the Examiner concedes, the Pirrung reference teaches mixtures of compounds ("indexed libraries"), not methods of making arrays of compounds in which each reaction vessel contains substantially only one compound. The Pirrung reference teaches that libraries of compounds can be prepared and screened as *mixtures*, although, as Pirrung teaches, deconvolution procedures are then needed to identify any active individual compounds within the library, and the individual compounds must then be resynthesized singly to confirm activity. In other words, the Pirrung reference teaches that synthesis and screening of *mixtures* is possible and even desirable, with synthesis of single compounds used only for confirmation of activity of individual actives.

The Gallop reference does not remedy the deficiencies of the Pirrung reference. The teachings cited by the Examiner do not, alone or in combination, provide any motivation for the skilled artisan to arrive at the claimed invention, in which arrays of compounds in solution are formed in reaction vessels and each reaction vessel contains substantially only one compound. Indeed, the Examiner points to teachings in the Gallop reference that refer to preparation and screening of *mixtures* of compounds prepared on *solid* supports (in the case of split synthesis as mixtures of beads, in the case of "tea-bag" synthesis as mixtures on resin support). The Gallop reference does not teach or suggest the claimed methods, in which, *inter alia*, arrays of compounds in solution are formed in reaction vessels and each reaction vessel contains substantially only one compound. These teachings cannot bridge the gap between the teachings of Pirrung and the claimed invention.

The Examiner's statement that the teachings of Gallop et al "motivate [the skilled artisan] to determine the number of individual compounds in a library depending on the number of reactants used each step, and the number of reaction steps in a reaction scheme" is not relevant. While the Gallop reference does refer to calculations for determining the number of compounds in a library, these teachings in no way suggest that the compounds should be made as single

compounds (as required by the pending claims) rather than as compound mixtures as described above.

Finally, the Examiner's statements in section 8 (page 9) of the Office Action must be addressed. The Examiner states that

> Pirrung et al teaches that the product mixtures were tested and their activities used as 'indices' to the rows or columns of a two dimensional matrix reflecting the activities of individual carbomates. a number of carbomates in the most active row and column ere synthesized and assayed demonstrating that the most active cell (refers to reaction vessel of the instant claims) in the matrix could be identified using sublibrary synthesis procedure.

Applicants do not agree with this characterization of the teachings of the Pirrung reference (even assuming *arguendo* that such teachings are enabling). Instead, the Pirrung reference states that "[t]he product *mixtures* were tested and their activities used as 'indices' to the rows or columns of a two-dimensional matrix reflecting the *activities* of individual carbamates." (emphasis added) Applicants contend that this statement does not indicate that the carbamates are present as single compounds, but rather that the compound *mixtures* are screened and then the *activities* are indexed in a matrix to determine the most active compounds. Thus, Applicants contend that the Examiner's subsequent statement (in the final paragraph of section 8 of the Office Action) that "Pirrung et al teach the advantages of the solution phase synthesis of compounds in an array" is incorrect. Similarly, the Examiner's statement that "it would have been obvious to one skilled in the art to combine the teachings of split pool synthesis method taught by Gallop et al with the indexed library synthesis taught by Pirrung et al" is unfounded, as the skilled artisan would have no motivation to combine the actual teachings of the references as stated by the Examiner.

For at least the above reasons, Applicants contend that the claimed invention is not rendered unpatentable by the cited references, either alone or in combination. Reconsideration and withdrawal of the rejection is proper and the same is requested.

Rejection of Claims Under 35 U.S.C. 103(a) over Pirrung and Rebek

Claims 10-13, 17-18, and 20-26 [sic] also stand rejected under 35 U.S.C. 103(a) as being unpatentable over the Pirrung et al. Advance ACS Abstract ("Pirrung") and Rebek, Jr. et al., U.S. Patent No. 5,877,030 (the "Rebek patent"). This rejection is traversed.

The teachings of Pirrung have been described above. The Examiner states that the Rebek patent teaches methods for forming combinatorial libraries by reacting a plurality of core molecules with a plurality of different tool molecules in solution.

The Examiner then states that

> it would have been obvious to a person skilled in the art . . . to use the different core molecules taught by Rebek Jr. et al with the indexed library synthesis method taught by Pirrung et al to obtain at least 500 different compounds. A person skilled in the art would have been motivated to use the indexed library of Pirrung et al to synthesize a combinatorial library of at least 500 different compounds in 500 reaction vessels or wells because Pirrung et al teach that the method can be prepared using any class of compounds and can be used for any type of assay because all compounds are generated in a free form with a single compound in each cell and Rebek Jr. et al teach the advantages of the use of different core structures with tool molecules to obtain more than thousand molecular diversity compound library.

Applicants respectfully traverse this rejection.

First, the deficiencies of the Pirrung reference have been noted *supra*. Applicants note that the Pirrung reference does not appear to teach or suggest, as the Examiner states in the just-quoted paragraph, that "all compounds are generated in a free form with a single compound in each cell." Instead, as described above, the Pirrung reference teaches, *not* that the carbamates are present as single compounds, but rather that the compound *mixtures* are screened and then the *activities* are indexed in a matrix to determine the most active compounds.

Second, the Rebek patent does not remedy the deficiencies in the teachings of the Pirrung reference. The Rebek patent, like the Pirrung reference, teaches that mixtures of compounds can be formed in solution; the Rebek patent does not teach or suggest the claimed methods for preparing arrays of compounds in solution, where the compounds are formed in reaction vessels and each reaction vessel contains substantially only one compound. Further, the Rebek patent teaches that the mixtures can be screened, *as mixtures*, to find any active compounds (see, e.g.,

Rebek patent, Examples 6-8 and 11).

Applicants respectfully urge that the skilled artisan would not be motivated to combine the teachings of the references, as stated by the Examiner. As described above, neither reference teaches or suggests the claimed methods; in fact, neither reference teaches or suggests that arrays of compounds can be formed in which each reaction vessel contains substantially only one compound, as required by the pending claims. Thus, no combination of the references can render the claimed invention unpatentable.

For at least the above reasons, Applicants contend that the claimed invention is not rendered unpatentable by the cited references, either alone or in combination. Reconsideration and withdrawal of the rejection is proper and the same is requested.

Correspondence Address

The Commissioner is respectfully requested to continue to direct all communication regarding this patent application to the attorneys of record:

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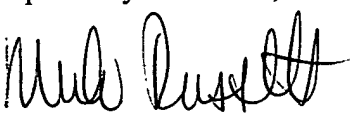
However, the Examiner is invited to call the undersigned if there are matters that need clarification regarding this filing.

The application is believed to be in condition for allowance. Applicants request any extension of time necessary for response. Although no additional fees are believed to be due, please charge any fees, or credit overpayments, to our deposit account No. 50-0647. If the Examiner considers that issues remain, a telephone call to the undersigned is invited.

Respectfully submitted,



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